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Ifosfamide, vincristine, doxorubicin and dacarbazine in adult patients with advanced soft-tissue sarcoma*

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Summary. A total of 37 adult patients with locally advanced or metastatic soft-tissue sarcoma (STS) entered a pilot study of combination chemotherapy based on the CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) regimen, in which cyclophosphamide was replaced by ifosfamide and mesna (1 g/m^2 ifosfamide given daily on days 1–5 as 2-h infusions, 1.5 mg/m^2 vincristine given on day 1 as a bolus injection, 50 mg/m^2 doxorubicin given on day 1 as a 5-min infusion, and 250 mg/m^2 dacarbazine given daily on days 1–5 as 30-min infusions). The overall response rate in 24 patients who were evaluable for response was 46% [95% confidence interval (CI), 25%–67%] and that in subjects who had not undergone prior chemotherapy was 50% (CI, 27%–73%). In all, 4 patients achieved a complete response (17%; CI, 5%–37%) and 2 remain in remission; 3 additional subjects were surgically rendered disease-free after they had shown a partial response. Overall, 31 patients were evaluable for toxicity. Toxicity was mainly hematological; in 3 patients the nadir WBC was $<0.5 \times 10^9$/l, and in 2 cases the nadir platelet count was $<50 \times 10^9$/l. During neutropenia, infections requiring intravenous antibiotics occurred in 8 patients (26%) and in 14 of 190 cycles (7.5%); 1 of these was fatal. We conclude that this new regimen offers promise for the treatment of advanced STS, producing acceptable toxicity.

Introduction

Successful chemotherapy for soft-tissue sarcomas (STS) has been limited by a lack of active drugs. Extensive work has been done to develop more effective forms of chemotherapeutic treatment. The most effective single agents are doxorubicin, dacarbazine (DTIC), and, more recently, ifosfamide. Response rates have been 18%–27% for doxorubicin [3, 5, 19], 16% for DTIC [17], and 18%–38% for ifosfamide [1, 6, 21]. The most widely used combination of agents has been the CYVADIC regimen (cyclophosphamide, vincristine, doxorubicin, and DTIC). Subsequent investigators have failed to reproduce the high response rates (50%) initially reported for this regimen [16, 18, 23]. Cyclophosphamide and vincristine, both of which are incorporated in the CYVADIC regimen, have shown no efficacy as single agents in adult STS [6, 15]. In a randomized trial, ifosfamide, a cyclophosphamide analogue, has been found to be superior to cyclophosphamide in the treatment of STS [6].

In view of both this finding and the promising results obtained using ifosfamide as a single agent, we decided to conduct a phase II trial based on the original CYVADIC regimen, in which cyclophosphamide was replaced by ifosfamide and mesna. This was termed the IVADIC regimen. The administration of ifosfamide with mesna (mercaptoethane sulfonate sodium) has been found to prevent the previously reported hemorrhagic cystitis [8].

Patients and methods

The eligibility criteria included histologically confirmed, inoperable metastatic or locally advanced STS, a WHO performance status of 0–2, an age of <75 years, and progressive, measurable disease. The histopathology was reviewed by one of us (M.V.). The patients were required to have adequate renal and hepatic function and bone marrow reserve. Prior chemotherapy was not an exclusion criterion. Informed consent was required.

A total of 37 consecutive patients have been treated since June 1988, of whom 9 failed to meet the eligibility criteria (2 subjects had a WHO performance status of more than grade 2, 1 patient was >75 years of age, 1 subject showed markedly elevated renal tests function prior to the beginning of treatment and did not complete the first cycle, and 5 patients were found to have bone sarcomas on review). All of the 4 patients with STS who were not eligible received a dose amounting to <50% of the scheduled dose; their tumors were evaluable for response and progressed early. Thus, 28 patients were eligible to participate in the present study.

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Table 1. IVADIC treatment schedule

Agent	Dose	Schedule
Ifosfamide	1 g m^{-2} day^{-1}	days 1–5
Vincristine	1.5 mg/m^2 (max. 2 mg)	day 1
Doxorubicin	50 mg/m^2	day 1
Dacarbazine	250 mg m^{-2} day^{-1}	days 1–5
Mesna	0.2 g m^{-2} × 3 day^{-1}	days 1–5

However, all treated patients were included in the toxicity analysis except six subjects who were not considered to be evaluable for toxicity due to major violations of the treatment protocol. These excluded patients had received a dose of ifosfamide, doxorubicin, and DTIC amounting to <70% (median, 47%, range, 33%–56%) of the prescribed dose during the first cycle and did not receive a higher dose during subsequent cycles. We chose this level of dose intensity in the present phase II study to demonstrate the toxicity of this specific regimen and thus defined a dose intensity of <70% at the start of treatment as a regimen different from the one studied. The excluded patients completed a total of 10 cycles; thus, 31 patients who had received 190 cycles were evaluable to toxicity. Of the 28 eligible patients, 24 were evaluable for response and had measurable disease. One patient had nonmeasurable disease. Another subject presenting with an inoperable undifferentiated sarcoma had received radiotherapy after the first cycle as part of a scheduled multimodality approach, prior to which a response had been observed. One additional patient lacked sufficient data for response evaluation, and another died of toxicity shortly after the end of the first 5-day infusion. Therapy continues in two of the evaluable patients, both of whom underwent surgery following a partial response.

The treatment schedule is shown in Table 1. The drugs were given over 5 days via a peripheral vein. Doxorubicin was given as a rapid (5-min) infusion in 100 ml saline, and vincristine was given as a bolus injection, after which DTIC dissolved in 500 ml saline was infused over 30 min. Patients were then given a short infusion of mesna in 100 ml saline followed by a 2-h infusion of ifosfamide in 500 ml saline. Thereafter, short infusions of mesna were given at 4 and 8 h after the start of the ifosfamide infusion. In the absence of emesis, the dose of mesna could be doubled and given per os. A new cycle was scheduled to begin on day 22.

In cases of prior extensive radiotherapy, the doses of ifosfamide and doxorubicin were reduced by 20%. The dose of ifosfamide was reduced by 20% in subsequent cycles if the nadir WBC was $<2.0 \times 10^9$/l, and it was increased by 20% if the nadir WBC was $>3.0 \times 10^9$/l. Doxorubicin was to be withheld after a cumulative dose of 500 mg/m^2 had been delivered.

Baseline investigations included a history and physical examination, determination of the performance status, tumor measurements, a complete blood cell count, a biochemical profile, urinalysis, an electrocardiogram, and a chest radiograph. Complete blood cell counts were performed at around day 14 of each cycle. Prior to the resumption of each cycle, a complete blood cell count and hepatic and renal function tests were carried out. Urinalysis was performed on days 3 and 5 of each cycle.

Response evaluations were made after alternate cycles, starting with the second cycle. In cases of lung metastases, a chest X-ray was taken before each treatment. The treatment response and the toxicity were assessed according to WHO criteria [14]. A "stable" response was noted only if the disease had remained stable for a minimum of two chemotherapy cycles. Response-rate CIs were calculated using exact binominal algorithms. The time to progression was calculated from the 1st day of chemotherapy to the date of documented progression. The time to progression and survival were calculated using the actuarial life-table method.

Table 2. Patients' characteristics and response

Patient number	Age (years)	Sex	Histologic diagnosis	Grade	Location of primary disease	Performance status (WHO)	Metastases	Primary or local recurrence	Response status	Time to progression (months)	Survival (months)	RT	CT
1	46	F	LMS	L	EXTR	0	+		CR	12+	12+		
2	20	F	EES	H	EXTR	0	+		CR	17	30+		
3	47	F	MFH	H	Orbit	1		R	CR	28+	28+		
4	38	F	EES	H	EXTR	0	+		CR	9	11+	+	
5	69	F	MFH	H	Neck	1	+	P	PR[a]	5+	5+		
6	36	M	MFH	H	Neck	0	+	R	PR	9	19+		
7	28	M	SS	H	EXTR	0	+		PR[a]	16	33+		
8	19	F	ARMS	H	EXTR	0	+	P	PR[a]	10	31		
9	42	M	LIS	L	EXTR	0	+	R	PR	8+	8+		
10	58	F	LMS	H	Uterus	0	+		PR	5	12		+
11	43	M	MFH	H	EXTR	1	+		PR	4	6	+	
12	33	M	NOS	H	EXTR	1	+	P	NC	2	6		+
13	38	M	NOS	H	EXTR	0	+		NC	2	9	+	
14	55	F	LIS	H	RETRO	1	+		NC	7	7	+	
15	30	M	NOS	H	EXTR	1	+	P	NC	2	5		
16	52	M	RMS	H	Bladder	2	+	R	NC	6	9		
17	37	F	LMS	H	Vena cava	1	+	R	NC	10	18	+	+
18	67	M	SS	H	EXTR	1	+	R	NC	3	3	+	+
19	42	F	NOS	H	EXTR	0	+		PD	1	10		
20	57	M	LIS	H	EXTR	1	+	R	PD	1	11	+	
21	69	F	LMS	L	Uterus	2	+		PD	2	7		
22	57	F	MFH	H	EXTR	0	+		PD	1	5		
23	29	M	NOS	H	Neck	0	+		PD	1	8	+	
24	60	F	NOS	H	RETRO	1	+		PD	1	7	+	

LMS, Leiomyosarcoma; EES, extraskeletal Ewing's sarcoma; MFH, malignant fibrous histiocytoma; SS, synovial sarcoma; RMS, rhabdomyosarcoma; ARMS, alveolar rhabdomyosarcoma; LIS, liposarcoma; NOS, sarcoma, not specified; H, high-grade primary; L, low-grade primary; EXTR, extremity; RETRO, retroperitoneum; P, primary; R, local recurrence; CR, complete response; PR, partial response; NC, stable disease; PD, progressive disease; RT, previous extensive radiotherapy; CT, prior chemotherapy

[a] Rendered disease-free by subsequent surgery

Table 3. Number and percentage of cycles, patients developing toxicity, and the severity of each toxicity

Cycle	N	WBC of $<0.5\times10^9$/l	WBC of $<1.0\times10^9$/l	Platelets count of $<50\times10^9$/l	Platelets count of $<100\times10^9$/l	Infection, grade 3–4	Nausea, grade 3	Median dose intensity			Median duration of cycle (days)
								A	I	D	
1	31	3%	13%	4%	4%	16%	35%	0.97	0.94	0.99	21
2	30	0	17%	0	0	7%	27%	0.96	0.79	0.96	24
3–5	70	3%	20%	2%	11%	6%	29%	0.95	0.81	0.95	26.5
6–8	36	6%	22%	3%	20%	6%	31%	0.95	0.75	0.93	28
9–11	17	0	14%	0	21%	6%	27%	0.8	0.73	0.96	27.5
All[b]	190	2.8%	18%	2%	11%	7%	31%	0.95	0.81	0.96	27
Individual[c]	31	10%	52%	7%	30%	25.8%	64.5%				

Percentages are based on patients from whom data were available. A, Doxorubicin; I, ifosfamide; D, DTIC

[a] Dose intensity = (delivered dose/m^2)/(scheduled dose/m^2)

[b] Percentage of cycles complicated by the specified toxicity

[c] Percentage of patients who experienced the specified toxicity

Results

The characteristics of patients who were evaluable for response are presented in Table 2. The median age of the subjects was 42.4 years (range, 19–69 years); 13 were women and 11 were men. Four of the individuals who were evaluable for response had previously received chemotherapy; in one case (patient 10, Table 2) it had been given in an adjuvant setting (cisplatin, epirubicin, and cyclophosphamide), and in three cases of advanced disease, prior treatment had involved sequential epirubicin and DTIC vs ifosfamide and etoposide [2]. Two of these subjects had also been treated with the CYVADIC regimen. Nine patients had previously undergone radiotherapy.

Toxicity

The number of cycles given, the hematological and gastrointestinal toxicities, and the treatment intensity are summarized in Table 3. After the first cycle, a reduction of >10% of the doxorubicin dose was undertaken in 10% of the patients, and such reductions in the DTIC and ifosfamide doses were carried out in 23% and 47% of the patients respectively. Leukopenia ($<0.5\times10^9$/l) developed in 3 patients (9.7%), 1 of whom had previously undergone extensive radiotherapy. Grade 3 thrombocytopenia developed in 2 subjects (6.7%), but no case of grade 4 thrombocytopenia was observed. One of these patients had previously received both radio- and chemotherapy. One patient died of septic shock during neutropenia, having failed to seek medical care before the 3rd febrile day. In all, 64% of the patients experienced grade 3 nausea. Since the introduction of the antiemetic agent tropisetron in February 1990, nausea has not been a major problem; prior to this, grade 3 nausea had been recorded in 41% of the cycles as compared with the current 14% ($P = 0.0001$, Mann-Whitney U-test).

Symptomatic vincristine neuropathy was recorded in six cases and resulted in the withdrawal of vincristine in these patients. One additional patient developed obstipation requiring medication. One subject experienced CNS toxicity, probably related to ifosfamide, during the fourth and fifth cycles of chemotherapy, after which treatment was discontinued. The symptoms were aphasia, dysphagia, and, during the fourth cycle, convulsions as well. This patient had also received radiotherapy to parts of his brain. After the discontinuation of ifosfamide, he recovered. Urotoxicity was not detected in any case. One patient experienced swelling of the parotid glands during two subsequent cycles but not during further cycles. A slight but insignificant and in every case transient rise in SGOT values was noted in several individuals. Alopecia was an invariable finding. Cardiac symptoms were registered in two patients. One 54-year-old woman developed acute atrial fibrillation and congestive heart failure during the first chemotherapy cycle. She had previously experienced episodes of acute atrial fibrillation for which she had received medication. At the time of chemotherapy she was off medication. She completed two further cycles without developing cardiac complications. Another patient (a 46-year-old woman) developed congestive heart failure at 2 months after the termination of chemotherapy, by which time she was in remission and had received a total dose of 540 mg/m^2 doxorubicin.

Response

In all, 11 of 24 evaluable patients responded [response rate, 46%; 95% CI, 26%–67% (when the ineligible patients with STS were included, the response rate was 39%)]. Of these, 4 achieved a complete response (17%; CI, 5%–37%). Another 3 subjects were surgically rendered disease-free after they had shown a partial response (after cycles 3, 6, and 6, respectively) that made the tumors operable. In 7 patients the disease remained stable (29%; CI, 13%–51%). The response rate in the 20 individuals who had not previously received chemotherapy was 50% (CI, 27%–73%). The patient who had previously received adjuvant chemotherapy achieved a partial response.

The median time to partial and complete responses were 6.9 and 18.4 weeks, respectively. The median time to progression for the evaluable patients was 5.0 months, with the value for partial responders being 9.0 months and that for complete responders, 17.7 months. Three patients remain disease-free, two following a complete response achieved by chemotherapy alone and one following the

surgical removal of a residual primary tumor after six cycles of chemotherapy. One subject developed CNS metastases after achieving a complete response, despite continuation of the response outside the CNS. The median survival was 9.6 months for eligible patients and 10.1 months for evaluable patients, with values of 8.0 months being recorded for those with progressive disease; 7.5 months, for those with stable disease; and 30.4 months for those showing a partial response. All four patients who achieved a complete response by chemotherapy alone are still alive (Table 2).

Discussion

Over the past two decades, the principal single agent used in the chemotherapy of advanced STS has been doxorubicin. A dose-response relationship for doxorubicin has been suggested in several studies [4, 16, 19]. However, the role of combination therapy in STS remains a matter of debate. Single-agent doxorubicin has been compared with doxorubicin- and DTIC-containing combination therapy in two larger randomized trials. The response rate for doxorubicin (50 mg/m^2) plus DTIC was significantly higher than that for doxorubicin alone (70 mg/m^2) [5]. The preliminary results of an EORTC (European Organization for Research and Treatment of Cancer) trial revealed no difference between the response rates for single-agent doxorubicin (75 mg/m^2) and those for doxorubicin (50 mg/m^2) combined with cyclophosphamide, vincristine, and DTIC (the CYVADIC regimen) [18]. Thus, the reduction in the dose of doxorubicin can at least be compensated by the addition of DTIC; moreover, the treatment period can be prolonged within the limits of cardiotoxicity. However, DTIC also adds toxicity, mainly gastrointestinal side effects.

In nonrandomized studies, the response rates for doxorubicin plus ifosfamide have been around 35% [9, 13, 20]. The preliminary results of two randomized studies reveal conflicting results. In the EORTC study, 75 mg/m^2 single-agent doxorubicin and the combination of 50 mg/m^2 doxorubicin (bolus) plus 5000 mg/m^2 ifosfamide (24-h infusion) produced comparable response rates [18], whereas in an ECOG (Eastern Cooperative Oncology Group) study, the response rate for ifosfamide (7.5 g/m^2 over 2 days) and doxorubicin (60 mg/m^2 over 2 days) was significantly higher than that for doxorubicin alone (80 mg/m^2) [10].

The natural conclusion of these observations is to combine DTIC, doxorubicin, and ifosfamide. This has been done at the Dana Farber Cancer Institute (MAID; 7500 mg/m^2 ifosfamide, 60 mg/m^2 doxorubicin, and 900 mg/m^2 DTIC, all given as continuous infusions over 3 days) [11] and by the Canadian Sarcoma Group (5000 mg/m^2 ifosfamide given as a 24-h infusion, 50 mg/m^2 doxorubicin given as an i.v. bolus, and 850 mg/m^2 DTIC given as a 1-h infusion) [7]. The response rate reported for MAID has been encouraging (47%; 95% CI, 37%–57%), but this regimen produces substantial toxicity and the dose intensity is significantly reduced during prolonged treatment. Nadir WBC values of $<0.5 \times 10^9$/l were detected in 26% of the cycles, platelet counts of $<50 \times 10^9$/l were noted in 21% of the cycles, and febrile episodes during neutropenia that required i.v. administration of antibiotics were recorded in 20% of the cycles. As chemotherapy in the majority of patients is at best palliative, although some of the complete responders may be long-term survivors [22, 24], the toxicity of this regimen would in many cases be unacceptable. The response rate for the Canadian regimen was 25% (95% CI, 13%–41%). Neutropenia of 0.5×10^9/l was recorded in 71% of the cycles, and 8% of the cycles were accompanied by neutropenic fever requiring i.v. antibiotics.

The rationale for our IVADIC regimen was the high response rates reported for the CYVADIC regimen and the documented superiority of ifosfamide to cyclophosphamide. As a supplement to the previously reported regimens, we added vincristine; however, the value of adding vincristine to doxorubicin has been questioned [19].

The dose intensity and hematological toxicity reported for the Canadian regimen are similar to those observed in our study. However, the initial doses in the MAID regimen were significantly higher, as was the hematological toxicity. The response rates for the IVADIC and MAID regimens were identical, whereas that for the Canadian study was much lower. Although the response rates obtained in these three phase II series and in previous studies on the CYVADIC regimen are not strictly comparable, the question arises as to whether the mode of administration of the agents, especially ifosfamide, might influence the efficacy. Preclinical data suggest that fractionated doses of ifosfamide are more effective than single doses against sarcomas [12]. Data from the phase II study by Antman and co-workers [1] also indicate that patients who received the 5-day bolus regimen responded better than those who received the same dose over 5 days by continuous infusion.

We conclude that the IVADIC regimen shows promising activity in advanced STS and produces comparably little toxicity. For a complete evaluation of the activity of this regimen, a randomized study comparing IVADIC (perhaps excluding vincristine) with ifosfamide plus doxorubicin is warranted.

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